REMARKS

Claim 33 has been amended to add back the numeral "33," thereby properly identifying this claim. This amendment is supported by original claim 33. No new matter has been added by way of this amendment. Claims 32, 33, 36, 37, and 58 are now currently pending.

Claim Objection:

Applicant respectfully submits that the objection to claim 33 has been obviated in light of the above amendments to claim 33. In particular, claim 33 has been amended to re-insert the proper claim number "33."

Claim Rejection:

Claims 58, 32, 36, and 37 remain rejected and Claim 33 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Volonté et al., J. Cell Biology 109:2395-2403 (Nov. 1989) ("Volonté") in view of Zhou et al., J. Biol. Chem. 275(4):2513-2519 (Jan. 2000) ("Zhou") and Benowitz et al., J. Biol. Chem. 273(45):29626-29634 (Nov. 1998) ("Benowitz").

To support this rejection, the Examiner asserts that the combined teachings of Volonté, Zhou, and Benowitz "suggest a relationship of N-kinase activity to neurite outgrowth in mammalian CNS neurons and further suggest a conservation of N-kinase structure across mammalian species" (Final Office Action, mailed June 12, 2006, at page 2). Applicant contends that, even if these references allegedly "suggest" a ***genera and undefined*** relationship between N-kinase activity and neurite outgrowth, such suggestion is merely speculative and is not sufficient to support an obviousness rejection of the claimed invention.

A proper *prima facie* showing of obviousness requires the Examiner to satisfy three requirements. First, the prior art relied upon, coupled with knowledge generally available to one of ordinary skill in the art, must contain some suggestion which would have motivated the skilled artisan to combine or modify references. *See In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the Examiner must show that, at the time the invention was made, the proposed modification had a reasonable expectation of success. *See Amgen v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Finally, the

modification or combination of references must teach or suggest each and every limitation of the claimed invention. *See In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). For the reasons discussed below, application of these standards to the present invention demonstrates that the Examiner has failed to establish even a *prima facie* case of obviousness.

The Examiner first described the combined teachings of Volonté, Benowitz, and Zhou in the Office Action mailed September 14, 2005. There, the Examiner conceded that these references were deficient in teaching several important aspects of the claimed invention (*see* Office Action, mailed September 14, 2005, at pages 4-5). For example, the Examiner admitted that, unlike the present invention, Volonté did not study ***human*** N-kinases or ***central nervous system*** ("CNS") neurons (*Id.* at page 4). Instead, Volonté described the partial isolation of a kinase from rat pheochromocytoma PC12 cells, and that this kinase was activated by nerve growth factor ("NGF") treatment of the PC12 cells and was sensitive to purine regulation (*see* Specification, at page 2, lines 1-4). Further, at the time of the present invention, the Volonté kinase (referred to therein as "protein kinase N") had been only partially purified and had not been molecularly characterized (*see id.* at page 2, lines 9-10).

To compensate for the deficiencies of Volonté, the Examiner has relied on the teaching of Benowitz. In particular, the Examiner has stated that Benowitz showed that 6-thioguanine ("6-TG")—i.e., one of the purine analogues reported in Volonté to inhibit N-kinase activity in the PC12 cells—inhibited axon outgrowth in rat retinal ganglion cells (Office Action, mailed September 14, 2005, at pages 4-5). However, a closer reading of Benowitz demonstrates the speculative nature of the Examiner's position. The focus of Benowitz was to study the role that purinergic compounds (e.g., purines) have in regulating growth and regeneration of neuronal connections (*see* Benowitz, at page 29626). The tissue used in the study was ***goldfish*** retinal ganglion cells. Benowitz acknowledged that many factors could be involved in regulating axonal outgrowth, and proposed the need for further study, stating:

> It will be of interest to identify the intracellular target(s) of the purines, whether it is protein kinase N or another molecule, and to characterize in detail the pathways that lead to axon growth.

(Benowitz, at page 29633, right column, last paragraph). Nowhere does Benowitz articulate that modulating N-kinase activity is critical in identifying compounds that modulate (i.e., either stimulate or inhibit) axonal outgrowth of a CNS neuron. Further, as noted by the Examiner (Office Action, mailed September 14, 2005, at page 5), Benowitz is deficient in that it does not teach the use of the ***human*** N-kinase.

In order to overcome the deficiencies of Benowitz, the Examiner cited Zhou as establishing that human and rat homologs of N-kinase were known to be structurally equivalent and that rat N-kinase was known to be expressed in CNS neurons (Office Action, mailed September 14, 2005, at page 5). However, Applicant asserts that such a comparison of structural equivalence and expression location is not sufficient to support this obviousness rejection. The N-kinase isoforms of Zhou are identified as "MST3b" and "MST3" (Zhou, at page 2513). Although the structural differences of these two isoforms were reported to be quite small (Zhou, at page 2516, right column), they exhibited distinct expression patterns (Zhou, at page 2513 and 2516). Further, only MST3b was shown to be brain-specific (Zhou, at page 2518, right column). Thus, the alleged structural and expression comparisons that the Examiner has made with regard to the human and rat N-kinase homologs, lacks any real persuasive weight. In addition, nowhere does Zhou identify MST3b as having a particular function, stating, for example:

> Study to identify endogenous substrates of this kinase will facilitate elucidation of the physiological significance of MST3b phosphorylation by PKA. (Zhou, at page 2518, left column.)
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> ** ** **
>
> The apparent high expression of MST3b in hippocampus and cerebral cortex may imply its potential functions involved in some important neurobiological activities. (Zhou, at page 2519, left column.)

As set forth above, Applicant respectfully submits that the combined teachings of Volonté, Benowtiz, and Zhou are not sufficient to support the obviousness rejection. Nowhere do the cited references teach or suggest that N-kinase is critical for axonal outgrowth of CNS neurons. As stated in the present application, prior to the present invention, a major deficiency in developing

treatments for CNS injuries was the lack of understanding of the molecules involved in mediating axonal outgrowth (*see* Specification, at page 2, lines 11-12). This deficiency in the prior art (including Volonté, Benowitzh, and Zhou) is exemplified by the following statements contained in the Summary of the Invention:

> The invention is based, at least in part, on the isolation of a highly purified form of the N-kinase polypeptide from normal mammalian neuronal tissue, molecular characterization of its chemical structure (including amino acid sequence), demonstration of its sensitivity to purine regulation and the discovery that this kinase plays an active role in the axonal outgrowth of CNS neurons, including mammalian CNS neurons, such as retinal ganglion neurons. Identification of N-kinase as a critical intracellular mediator of axonal outgrowth, and chemical characterization of its structure, now provides for the ability to modulate axonal outgrowth by modulating N-kinase activity. Furthermore, this purification and characterization of N-kinase now allows for its use in screening assays to identify additional modulators of axonal outgrowth.

(Specification, at page 2, lines 18-30.)

As shown above, prior to the present invention, the critical role of N-kinase in mediating axonal outgrowth was not known. Without such knowledge, Applicant asserts that combining and modifying Volonté, Benowitz, and Zhou in order to practice the claimed invention would not have been reasonably expected to succeed at the time of the present invention. In view of all of the deficiencies in the prior art mentioned above, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

Accordingly, Applicant respectfully requests that the renewed rejection of claims 58, 32, 36, and 37, and the new rejection of claim 33 under 35 U.S.C. 103(a) be withdrawn.

In view of the foregoing, Applicant respectfully requests favorable reconsideration of the application.

The Examiner is authorized to charge any fee deficiencies or credit any overpayments associated with this submission to the Nixon Peabody LLP Deposit Account No. 50-0850.

Application No. 09/656,915
Amendment dated September 12, 2006
Response to Final Office Action of June 12, 2006

The Examiner is invited to contact the undersigned if further matters need to be discussed in order to expedite the prosecution of the present application.

Date: 9/12/06

Respectfully submitted,

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